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EXAMINER	
NOGUEROLA, ALEXANDER STEPHAN	
ART UNIT	**PAPER NUMBER**
1753	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

5

Office Action Summary	Application No.	Applicant(s)
	10/629,970	RAMSEY ET AL.
	Examiner	**Art Unit**
	ALEX NOGUEROLA	1753

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-35,53,55 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-35,53,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Objections and Rejections pending since the Office action of July 22, 2005

1. All previous rejections under 35 U.S.C. 112, first paragraph, are withdrawn, but these rejections have been rewritten in light of Applicants' amendment or restated below for Applicants' convenience. Note the new rejection of claim 14 under 35 U.S.C. 112, first paragraph.

2. The rejection of claim 43 under 35 U.S.C. 112, second paragraph, is withdrawn.

3. All rejections under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) are withdrawn.

4. All previous rejections under 35 U.S.C. 103(a) are withdrawn, except for the rejections of claims 25-33 as being obvious under 35 U.S.C. 103(a) over Guo in view of Lee, which are maintained and restated below for Applicants' convenience.

5. The objection to the specification is withdrawn.

Response to Arguments

6. Applicant's arguments filed December 27, 2005 ("Amendment') have been fully considered but they are not persuasive.

<u>*A. Rejections under 35 U.S.C. 112, first paragraph*</u>

It should be first noted that Applicants inadvertently forgot to mention the rejection of claim 34 under 35 U.S.C. 112, first paragraph, on page 34 of the Office action of July 22, 2005 ("Office Action").

Applicants state, "In the present case, the examiner has done no more than merely assert that undue experimentation would be required to practice the full scope of applicants' invention." Page 14 of Amendment. The examiner respectfully disagrees. The examiner has addressed in detail all of the "Wands" factors, which are recognized as useful in determining whether the disclosure in question requires undue expermerimentation in order to practice the claimed invention. See MPEP 2164.01(a)

Applicants state, "The present invention allows one to take a device having a dimension of width or depth on the order of <u>100 nanometers</u>, for example, and reduce it to a smaller dimension in a controlled fashion by the applicant of an appropriate thickness of coating material [emphasis added]." Page 15 of the Amendment. Nowhere

in the claims is the nano-opening or nano-channel to be coated required to have a width or depth of 100 nanometers or greater. Furthermore, as pointed out on pages 3-4 of the Office Action, the techniques disclosed by Applicants have lower limits to the dimensions of nanochannels that can be made; or are used to form a different type of nanostructure that claimed, such as Li who forms a nanometer scale hole through a substrate; or are time-consuming, complex, and prone to non-uniformities, such as the technique of Guo.

Applicants' disclosure for coating the nanochannel, as discussed on pages 4-5 of the Office action, applies to very different structures from that being claimed. For example, "Dubas (page 13 of the specification from polyelectrolyte multilayers on a *flat* silicon wafer" and "Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3mm and one with an inner diameter of 0.2 mm. See Figures 1-3."

Applicants cite on page 15 of the Amendment an article by Stjernstrom and Roeraade for teaching how to enclose the nanochannel(s) with a cover member. However, this article does not appear to be of record in the original disclosure. Furthermore, Applicants' comment that this article discloses wafer bonding. Guo discloses, as mentioned on page 4 of the Office Action, limited use for wafer bonding in commercial applications. Also, for nanofluidic channels 100nm or less wafer bonding often results in the partial or complete filling of the channel.

Applicants state at the bottom of page 15 of the Amendment bridging to page 16, "As for the examiner's query concerning how pressure or vacuum is to be created in the

uncovered nanochannel, the simple answer is that it isn't ... See, for example, the surface modification technique described in the paragraph bridging pages 14-15 of the specification. This technique would be applicable, for example, when implementing the method claimed in claim 3." However, "... the surface modification technique described in the paragraph bridging pages 14-15 of the specification..." involves oxidizing a silicon surface. Claim 1 makes no reference to silicon or an oxidizable surface. None of the other claims refer to oxidizing a silicon surface to form a nanocoating. Furthermore, claims 1 and 3 have steps of *applying a coating material*, which from Applicants' original disclosure would be understood to mean organic molecular coatings, particularly on a plastic substrate. See pages 10 and 13 of 14 of the specification and claims 10, 15, and 16. The claims, thus, are at variance with the, "... the surface modification technique described in the paragraph bridging pages 14-15 of the specification..."

Applicants state, "Concerning claims 20 and 21, the use of resist layers in the fabrication of nano-scale structures is quite common, as a Google search will readily reveal." Such a statement falls far short of meeting the written description (new matter) and enablement requirements under 35 U.S.C. 112, first paragraph. Furthermore, as stated on page 7 of the Office Action, 'For clam 21, note again, as stated by Guo, "... the removal of the sacrificial layer in nano-channels is non-trivial."'

With respect to U.S. Patents Nos. 5,858,195 and 6,001,229 discussed on page 16 and also at the bottom of page 17, bridging to page 18 of the Amendment, Applicants first acknowledge that these patents do not disclose nanochannels, but then state, "Rather, the '195 and '229 patents are cited for their disclosure of

electrokinetically driving coating materials, such as polyelectrolytes disclosed at page 13, lines 12-18, through the nanochannel(s) in order to coat the surface thereof." On what basis can it be reasonably assumed that the techniques of '195 and '229 for coating microchannels can be used to also coat nanochannels? Furthermore, as point out on page 6 of the Office Action the techniques of these patents require a covered nanochannel, while claim 1 requires the nanochannel to be uncovered when the coating is applied.

With regard to claim 6, Applicants refer to U.S. Patent 6,294,223 for providing enablement for creating a coating on a nanochannel. '223 is not mentioned in the original disclosure. Furthermore, '223 is non-analogous art as it states,

> This invention relates generally to the field of alteration of the optical properties ceramic materials via ion implantation, and more particularly to a method for ion implantation induced embedded particle formation via a chemical reduction mechanism. The invention is concerned with ion implantation into a substrate material involving controlled formation of small size (~10nm) particles within a substrate material wherein the particles are primarily composed of the atoms of the substrate material." See col. 1:25-35.

With regard to claim 11, as with claim 6, Applicants seek enablement outside the original disclosure, as the Lin et al. article and Sun and Kiang book excerpt mentioned on page 17 of the Amendment are newly cited. Also, Lin et al. concerns a flat silicon substrate and the Sun and Kiang publication was published in 2005, which is after Applicants' filing date.

.B. Rejections of claims 25-33 as being obvious under 35 U.S.C. 103(a) over Guo in view of Lee.

Applicants acknowledge that the nanofluidic channels are "for a wide range of applications," but then assert that the application of Lee is not included in this range. While it is true that "the electro-osmotic flow applications apparently contemplated by Guo et al. ... do not require an electrically conductive conduit, which is essential for the application described by Lee et al., Guo also states in the same paragraph regarding electro-osmotic flow, "In addition, nanofluidic channels are a new emerging area where many potential applications can be exploited." See paragraph [0026]. The application of Lee is one such application because unlike electrophoresis and electrosmotic methods contemplated by Guo, which involve charged molecules, such as DNA, the application of Lee allows reversible transport of *neutral* molecules. See the second full paragraph in the first column on page 11850. Also, since the gold nanotubes are very thin the additional manufacturing cost would not be much more then without out. In any event any extra cost would be justified if the value of the molecules to be transported is high, such as an expensive pharmaceutical compound.

Applicants allege that the use of Lee to modify Guo is hindsight reasoning. Where do Applicants disclose electromodulated molecular transport of neutral molecules in gold-nanotubes?

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 3, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 3 requires "enclosing said nanochannel with an uncoated cover member after applying said coating material, said channel having a second depth reduced by approximately said defined thickness." Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 3, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 3 and the last two paragraph at the bottom of page 11 of the specification. Also,

"The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at the nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to enclosing the nanochanel with a cover member,

'... known methods of constructing sealed "micron-scale' fluidic channels typically include anodic bonding of a glass coverslip or soft elastomeric material to prefabricated channels on a substrate. The high temperature and high voltages typically used in the anodic bonding process greatly limit the process to commercial applications; while the bonding of soft elastomeric material, such as PDMS, to nanofluidic channels being about 100nm or less in size often results in the partial or complete filling of the channel due to the rubber-like behavior of the

soft elastomeric material." (paragraph [0004] in Guo et al. (US 2003/0209314 A1)).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer; and

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As

the scale of structures approaches molecular scale new phenomena arise that must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Looking closely now, for example, at some of the references cited for guidance of forming a coating in the nanochannel, in addition to the comments above on the disclosed references on forming a coating in the nanochannel, it should be noted that neither U.S. Patents 5,858,195 nor 6,001,229 appear to disclose coating even the walls of a *microchannel* by using electrokinetically driven flow, let alone a nanochannel having three walls. Page 14 of the specification state.

> Coating reagents can also be transported through the channels to be coated by using hydraulic means. For example pressure can be applied to a reagent reservoir, attached directly of indirectly to a nanochannel, using a syringe pump or by applying a vacuum to the terminus of the nanochannel.

But Claims 3 requires enclosing the nanochannel with an uncoated cover member *after* applying the coating material. So how is pressure or a vacuum to be created in the uncovered nanochannel?

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device. More particularly, undue experimentation would be required for coating a nano-opening having three wall surfaces forming a substantially rectangular, open nanochannel. A technique used to coat a nanochannel with a circular cross section is not necessarily easily adapted for coating a nanochannel with a rectangular cross-section.

For claim 21, note again, as stated by Guo, "... the removal of the sacrificial layer in nano-channels is non-trivial."

9. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

The rejection of claim 3 above under 35 U.S.C. 112, first paragraph, applies also to claim 4.

10. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
Claim 6 requires applying a coating material having a defined thickness by ion implantation. Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 6, a

process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, the dimensions of the nanochannel, or the possible range of the defined coating thickness. See Claim 6 and the last two paragraph at the bottom of page 11 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at the nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter. However, none of these references involve ion beam implantation.

Jirage (page 12 of the specification) first uses electroless gold deposition to form an Au coating and the chemisorption to form a thiol linked coating inside nanochannel (see the Jirage abstract);

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer by spin coating (see the Dubas abstract);

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels nor electrically driven coating as asserted; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill.

The level of predictability is not high. While techniques used in manufacturing

and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise that must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide no guidance on forming a coating by ion implantation. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, <u>in theory,</u> can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that <u>might</u> be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device by effecting the step of applying the coating by ion implantation. More particularly, undue experimentation would be required for coating a nano-opening having three wall surfaces forming a substantially rectangular, open nanochannel. A technique used to nanocoat a flat plate, for example, is not necessarily easily adapted for coating a nanochannel with a rectangular cross-section.

11. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 11 requires the molecular film to be covalently attached to the solid substrate.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 11, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 11 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to enclosing the nanochanel with a cover member,

'... known methods of constructing sealed "micron-scale' fluidic channels typically include anodic bonding of a glass coverslip or soft elastomeric material to prefabricated channels on a substrate. The high temperature and high voltages typically used in the anodic bonding process greatly limit the process to commercial applications; while the bonding of soft elastomeric material, such as PDMS, to nanofluidic channels being about 100nm or less in size often results in the partial or complete filling of the channel due to the rubber-like behavior of the soft elastomeric material." (paragraph [0004] in Guo et al. (US 2003/0209314 A1)).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*lfuidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. Only one, Hjerten, discloses covalently attaching the molecular film to the

substrate. However, as noted above, the inner diameters of the capillaries used by Hjerten are 0.2 mm and 3 mm, which are several orders of magnitude larger than a nanometer channel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method

12. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 6 requires coating the three wall surfaces by converting silicon to silicon oxide. Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 14, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, the dimensions of the nanochannel, or the possible range of the defined coating thickness. See Claim 14 and the last two paragraphs at the bottom of page 11 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at the nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel by chemical converting silicon to silicon oxide,

Applicants cite several prior art references allegedly relevant to coating a nanochannel. However, none of these references involve chemically converting silicon to silicon oxide.

Jirage (page 12 of the specification) first uses electroless gold deposition to form an Au coating and the chemisorption to form a thiol linked coating inside nanochannel (see the Jirage abstract);

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer by spin coating (see the Dubas abstract);

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels nor electrically driven coating as asserted; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

The only reference to chemically converting silicon to silicon oxide in the original disclosure is a paragraph at the bottom of page 14, bridging to page 15 of the specification. This paragraph is highly speculative. Even if the unreferenced formula of a silicon oxide thickness of 1.56 X nm resulting from converting X nm thickness of a silicon surface to silicon oxide by oxidation is accurate there is no evidence that this formula can be applied to a nanochannel formed by three walls. That is, there is a substantial difference between growing a silicon oxide layer on a planar silicon surface and growing a controlled silicon layer on three sides of a nanoscale channel.

One with ordinary skill in the art would have a high degree of skill.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise that must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide no guidance on forming a coating by converting silicon to silicon oxide. Applicants rely on various prior art references as guidance on forming the

nanochannel and the coating in the nanochannel, none of which concern converting silicon to silicon oxide.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, <u>in theory,</u> can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that <u>might</u> be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] <u>should</u> be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device having a three-walled nanochannel by converting silicon to silicon oxide.

13. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 17 requires applying an additional polyelectrolyte coating that has the opposite charge of the polyelectrolyte to which it is applied.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 17, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 17 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to <u>any</u> nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic

microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*lfuidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be

considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. Most particularly, as noted above, Dubas, which discuses applying polyelectrolyte multilayers, is about coating a flat substrate, not a channel, let alone a nanochannel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, <u>in theory,</u> can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that <u>might</u> be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] <u>should</u> be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device.

14. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 19 requires the substrate to have both the open nanochannel and a microchannel having a free space with a third cross-sectional area greater than the first cross-sectional area, the microchannel being connected to the nanochannel.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 19, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 3 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to <u>any</u>

nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanolfuidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer; and

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may

be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Looking closely now, for example, at some of the references cited for guidance of forming a coating in the nanochannel, in addition to the comments above on the disclosed references on forming a coating in the nanochannel, it should be noted that neither U.S. Patents 5,858,195 nor 6,001,229 appear to disclose coating even the walls of a *microchannel* by using electrokinetically driven flow. Page 14 of the specification state.

> Coating reagents can also be transported through the channels to be coated by using hydraulic means. For example pressure can be applied to a reagent reservoir, attached directly of indirectly to a nanochannel, using a syringe pump or by applying a vacuum to the terminus of the nanochannel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, <u>in theory,</u> can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that <u>might</u> be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] <u>should</u> be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method

15. Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claims 22-24 require the step of "applying a planar cover member to said uncovered surface overlying said coated, open flow channel to hereby close the top of said flow channel and form said nanometer-scale conduit." Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 22, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the

nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 22 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to <u>any</u> nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be

considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Looking closely now, for example, at some of the references cited for guidance of forming a coating in the nanochannel, in addition to the comments above on the disclosed references on forming a coating in the nanochannel, it should be noted that neither U.S. Patents 5,858,195 nor 6,001,229 appear to disclose coating even the walls of a *microchannel* by using electrokinetically driven flow. Page 14 of the specification state.

> Coating reagents can also be transported through the channels to be coated by using hydraulic means. For example pressure can be applied to a reagent reservoir, attached directly of indirectly to a nanochannel, using a syringe pump or by applying a vacuum to the terminus of the nanochannel.

But Claims 22 requires enclosing the nanochannel with a planar cover member *after* applying the coating material. So how is pressure or a vacuum to be created in the uncovered nanochannel?

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device.

For claim 23 also note that in regard to chemical etching Applicants merely state, "Features of similar length scale [10 nm] can then by machined in a substrate using either wet (solution) or dry (plasma) etching techniques. See page 5 of the specification.

For claim 24 also note that in regard to ion beam milling Applicants state this approach "*might* be effective [emphasis added]", and acknowledge, "In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm," (page 5 of the specification) and that Li et al. "forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (page 6 of the specification).

16. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention. The rejection of claim 17, above, can largely be also applied to claim 34 since the unenabled aspect of all of these claims is a coating comprising a plurality of layers of polyelectrolyte material, each layer being opposite in charge to its adjacent layer.

17. Claims 35 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 35 requires the lateral dimension of the coated nanometer-scale conduit to be approximately one nanometer. Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 35 is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 35 and the last two paragraphs at the bottom of page 11 of the specification. Also, "The invention has applicability to <u>any</u> nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*lfuidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be

considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. What little guidance is provided actually teaches away from the claimed invention. The discussion on page 12 of the specification regarding forming nano-openings only mentions making holes of 5 nanometers, not approximately 1 nm as claimed. Also, a hole is not an open channel, with a bottom wall and side walls as required by claim 25. Jirage, which is cited on page 12 of the specification, only discloses "reducing the cross-sectional area from 100 nm^2 to 10 nm^2." Page 14 of the specification states, "A single polyelectrolyte layer has a thickness ranging from approximately 1 nm to a few tens of nanometers and multilayer film thicknesses of approximately 1 micron have been formed." So even if a polyelectrolyte layer could be coated into a nanochannel using the disclosed techniques there is a question as to whether the thickness can be controlled to give an opening with a lateral dimension of approximately one nanometer.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, <u>in theory,</u> can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that <u>might</u> be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] <u>should</u> be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to make the claimed device.

18. Claims 53, 55, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claims 53, 55, and 56 require using an electrical force for modifying the coating in one way or another.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claims 54-56, process of making claims, are very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 54-56 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to <u>any</u> nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer; and

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*lfuidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may

be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Applicants seem to rely on an informal incorporation by reference of U.S. Patents Nos. 5,858,195 and 6,001,229 for support/explanation of for claims 54-56 (See page 13 of the specification, last paragraph); however, the examiner has not found in either patent a discussion of using electrokinetic force to coat a microchannel, let alone a nanochannel. "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of disclosure as required by 35 U.S.C. 112, first paragraph. Particular attention should be directed to specific portions of the reference document where the subject matter being incorporated may be found." See MPEP 608.1(p).I.A.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, <u>in theory,</u> can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that <u>might</u> be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It <u>may</u> also be possible to use proximal probe techniques to perform lithography " (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] <u>should</u> be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed methods

19. Note that dependent claims will have the deficiencies of base and intervening claims.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1, 4, 7-10, 12, 13, 15, 16, 18, and 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (US 203/0209314 A1) ("Guo") in view of Lee et al. ("Electromodulated Molecular Transport in Gold-Nanotube Membranes," J. AM. CHEM. Soc. 1002, 124, 11850-1851") ("Lee").

Addressing claim 1, Guo discloses

a. providing a solid substrate including a nano-opening defined by at least three wall surfaces fabricated in the substrate, the nano-opening having a given first cross-sectional area of nanometer-scale dimensions bounded by the at least three wall surfaces, the three wall surfaces forming a substantially rectangular, open nanochannel having a first width and a first depth (se the abstract and Figure 1);

b. enclosing the nanochannel with a cover member (Figure 1).

Guo does not mention "applying a coating material having a defined thickness to the at least three wall surfaces, thereby causing the nano-opening to have a second cross-sectional area of nanometer-scale dimensions reduced relative to the first cross-sectional area."

Lee discloses applying a coating material having a defined thickness to a nanochannel, thereby causing the nano-opening to have a second cross-sectional area of nanometer-scale dimensions reduced relative to a previous cross-sectional area. It would have been obvious to one with ordinary skill in the art at the time of the invention to apply a coating as taught by Lee in the invention of Guo because Guo discloses electro-osmotic flow of molecules (paragraphs [0002] and [0026]) as taught by Lee the coating can be used to reversibly control the flow of neutral molecules through the nanometer-scale conduit. The coating can be easily removed by applying an appropriate potential across the nanochannels and a new coating or no coating used. See the second full paragraph in the first column on page 11850 and Figure 1.

As for the coating material reducing the free space between the opposed sidewalls by a factor of approximately two times the defined thickness this would be

inherent if a coating of approximately the same thickness (See Figure 1 of Lee) is applied to the sidewalls in Guo.

Addressing claim 4, it would have been obvious to one with ordinary skill in the art at the time of the invention to provide a fourth wall, such as the substrate in Figure 1 of Guo, to bound the first cross-sectional area prior to applying the coating material because it would be easier to coat all four nanochannel walls when the nanochannel is enclosed, just introduce coating solution in the channel and apply an appropriate potential across the channel. See the second paragraph in the first column on page 11850.

Addressing claims 7, 12, and 13, in Guo as modified by Lee the forming the coating involves by chemisorption, which is a type of non-covalent film deposition that chemically converts the solid substrate material. See the second paragraph in the first column on page 11850.

Addressing claim 8, in Guo as modified by Lee the coating includes a nanometer-scale gold coating. See Figure 1.

Addressing claims 9 and 10, for the additional limitations of these claims see in Lee Figure 1.

Addressing claim 15, for the additional limitations of this claim see in Lee Figure 1.

Addressing claim 16, although Figure 1 of Lee only shows a monoelectrolyte material, as recognized by Lee, "... it seems likely that more sophisticated forms of transport selectivity might be possible. For example, by making ionic versions of molecule-specific complexing agents (e.g., cyclodextrins), it might be possible to electromodulate transport of the molecules that bind to these agents." See the last paragraph of the article. Furthermore, numerous polymeric materials were used at the time of the invention as capillary coatings to control electro-osmotic flow. Thus, the use of a polyelectrolyte material in the coating just depends on the desired electromodulation of the fluid.

Addressing claim 18, for the additional limitations of this claim see in Lee Figures 1 and 3.

Addressing claim 25, Guo discloses a nanostructured device for use in transporting a fluid medium having components of differing lateral dimension (abstract; Figure 5; and paragraph [0002]), the device having a nanometer-scale conduit (Figure

5) and comprising a solid substrate having an upper surface (Figure 5), a nanochannel having a bottom wall spaced below the upper surface and opposed side walls (Figure 5), the nanochannel having a given first cross-sectional channel area of nanometer scale dimensions defined by the free space between the opposed side walls and the depth of the bottom wall below the upper surface (Figure 5), and a planar cover member on the upper surface overlying the nanochannel, which closes the top of the channel and forms the nanometer-scale conduit (Figure 5).

Guo does not mention a coating as claimed.

Lee discloses a coating for a fluidic nanotube. See Figure 1. It would have been obvious to one with ordinary skill in the art at the time of the invention to provide a coating as taught by Lee in the invention of Guo because Guo discloses electro-osmotic flow of molecules (paragraphs [0002] and [0026]) as taught by Lee the coating can be used to control the flow of molecules through the nanometer-scale conduit. See the second full paragraph in the first column on page 11850 and Figure 1.

As for the coating material reducing the free space between the opposed sidewalls by a factor of approximately two times the defined thickness this would be inherent if a coating of approximately the same thickness (See Figure 1 of Lee) is applied to the sidewalls in Guo.

Addressing claim 26, for the additional limitations of this claim see in Guo Figure 5 and paragraph [0027].

Addressing claim 27, although not stated the nanochannel in Figure 5 of Guo clearly acts as a bottleneck that would affect the rate of transport of fluid medium as claimed.

Addressing claim 28, since claim 25 does not require a fluid medium, it is an intended, claim 28 does not further structurally limit claim 25 and can be rejected on the same basis as claim 25. Furthermore, the device of Guo can used as intended by Applicants.

Addressing claims 29-32, for the additional limitations of these claims see in Lee Figure 1.

Addressing claim 33, although Figure 1 of Lee only shows a monoelectrolyte material, as recognized by Lee, "... it seems likely that more sophisticated forms of transport selectivity might be possible. For example, by making ionic versions of molecule-specific complexing agents (e.g., cyclodextrins), it might be possible to electromodulate transport of the molecules that bind to these agents." See the last paragraph of the article. Furthermore, numerous polymeric materials were used at the time of the invention as capillary coatings to control electro-osmotic flow. Thus, the use

of a polyeclectrolyte material in the coating just depends on the desired electromodulation of the fluid.

Final Rejection

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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AU 1753
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